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Note

Ocular sustained delivery of prednisolone using hyaluronic acid benzyl ester films

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Abstract

Hyaluronic acid benzyl ester films were studied for ocular delivery of prednisolone. The four polymers used were HYAFF 11 p25 (25% benzyl ester, 75% sodium salt), HYAFF 11 p50 (50% benzyl ester, 50% sodium salt), HYAFF 11 p75 (75% benzyl ester, 25% sodium salt) and HYAFF 11 (100% benzyl ester). The polymer with the lowest degree of esterification, HYAFF 11 p25, was the most hydrophilic and released drug faster than those with higher degrees of esterification, HYAFF 11 and HYAFF 11 p75, which are generally less hydrophilic. Tear fluid prednisolone concentrations were measured in rabbits after administration of the test films. Areas under the tear fluid concentration vs time curves ($AUC_{0-8\,h}$) were calculated for all the dosage forms, from the time of dosing to 8 h post-dosing. The HYAFF 11 p25 films provided higher initial concentrations which rapidly declined below 30 μg/ml, 2 h post-dosing. Concentrations for the HYAFF 11 p75 film dropped below 30 μg/ml, 3 h post-dosing. The HYAFF 11 films provided the best results with sustained concentrations between 45 and 72 μg/ml for the 8 h study period. The results show that sustained delivery of prednisolone to the eye may be achieved with the use of hyaluronic acid esters.

Keywords: Hyaluronic acid; Hyaluronate benzyl ester; Ophthalmic sustained release; Prednisolone ocular delivery

Continuous delivery of drugs to the eye offers major advantages over conventional ocular therapies that involve administration of drug solutions or suspensions as eye drops. Eye drop administration often results in poor bioavailability and therapeutic response due to rapid precorneal elimination of the drug and is also associated with patient compliance problems (Schoenwald, 1990). An ocular sustained release dosage form would ideally eliminate these problems by providing steady precorneal drug levels for 12–24 h periods. Selection of an appropriate matrix for sustained release dosage forms is critical to their performance. Hyaluronic acid is a major component of the aqueous and vitreous humors in the eye

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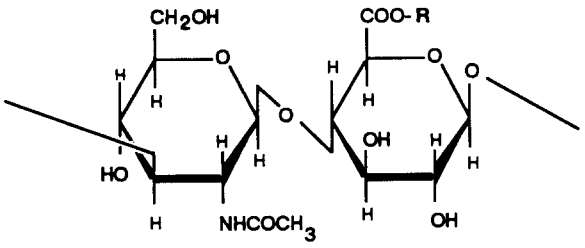

Fig. 1. Structure of the repeating unit of hyaluronic acid esters. 'R' groups are the benzyl or the sodium salt.

(Saettone et al., 1991) and offers a potentially biocompatible and biodegradable matrix for fabrication of ocular sustained release dosage forms. Various esters of hyaluronic acid have been prepared as a means of altering its physicochemical properties while maintaining its pharmacological advantages as well as biocompatibility (Della Valle et al., 1987). Dosage forms based on the benzyl esters of hyaluronic acid have been used in our laboratories for ophthalmic sustained release of methylprednisolone in rabbits. They were shown to increase drug bioavailability when compared to a suspension formulation (Kyyrönen et al., 1992). Dosage forms based on a similar polysaccharide, gellan, were also shown to provide sustained tear fluid levels of methylprednisolone in rabbits when compared to conventional formulations (Sanzgiri et al., 1993). While methylprednisolone was used as a model steroid drug in these studies, prednisolone, alone or in conjunction with other drugs, is predominantly used in clinical practice for treatment of ocular inflammation (McEvoy, 1993). The aim of this study was to demonstrate sustained precorneal tear fluid drug levels in rabbits following ocular administration of prednisolone-loaded hyaluronate ester films.

The hyaluronic acid esters, namely, HYAFF 11 p25 (25% benzyl ester, 75% sodium salt), HYAFF 11 p50 (50% benzyl ester, 50% sodium salt), HYAFF 11 p75 (75% benzyl ester, 25% sodium salt) and HYAFF 11 (100% benzyl ester), were provided by FIDIA S.p.A. (Padova, Italy). The structure of these esters is shown in Fig. 1.

Films containing physically dispersed prednisolone (Sigma Chemical Co., St. Louis, MO) were prepared as described by Hunt et al. (1990). The respective polymer-prednisolone combinations were dissolved in solvent, poured onto glass plates and dried at low power in a microwave oven. Circular pieces of the films, 4 mm in diameter, were used for drug content determination and in vivo studies. Each film contained 270 ± 54 μg of prednisolone, as determined by extraction of the drug into a pH 10 borate buffer and analysis by HPLC.

Male New Zealand rabbits weighing 2.8–4.1 kg were used to measure the in vivo release of prednisolone in tear fluid. The rabbits were placed in restraining boxes during the experiment but free head and eye movement was allowed. The test films were administered on the upper corneoscleral limbus of the left eye of each rabbit with a pair of forceps. Tear fluid samples were collected from the lower marginal tear strip using 1 μl disposable glass capillaries (Drummond 'Microcaps', Fisher Scientific, St. Louis, MO) as described by Urtti et al. (1990). Prednisolone analysis was carried out using a reverse-phase HPLC assay described by Kyyrönen et al. (1992) for quantitation of methylprednisolone. Peak areas were measured and concentrations determined using a calibration curve of standard prednisolone solutions.

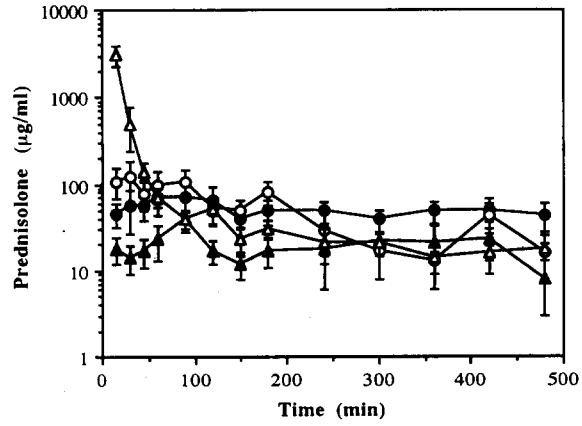

Fig. 2. Tear fluid prednisolone concentration vs time profiles seen following administration of HYAFF 11 film (●), HYAFF 11 p75 film (○), HYAFF 11 p50 film (▲) and HYAFF 11 p25 film (△). Means ± S.E. are presented ($n = 6$–9).

The tear fluid levels of prednisolone measured after administration of the various test films are shown in Fig. 2. Areas under the prednisolone tear fluid concentration vs time curves ($AUC_{0-8\,h}$) were calculated for the tear fluid data using the linear trapezoidal rule (Gibaldi et al., 1982), and are listed in Table 1. $AUC_{0-8\,h}$ provides a measure of the total precorneal exposure to the drug. The relative contributions from the early (0–2 h) and late (2–8 h) phases of the tear fluid profiles to the total AUC were calculated to estimate and compare the release sustaining effect of the films. A desirable tear fluid profile would consist of a minor contribution from the early phase and a major contribution from the later phase to its total AUC. This would indicate that a small proportion of the total drug was released immediately while a majority of the drug was released in a prolonged manner.

The film made from HYAFF 11 p25, the most hydrophilic polymer of the series, provided a high initial peak followed by a rapid drop below 30 μg/ml approx. 2 h post-dosing. As seen in Table 1, the drug concentrations over the first 2 h accounted for 85% of the total $AUC_{0-8\,h}$ value, whereas the remaining 6 h contributed only 15% of the total AUC. Thus, a very poor sustaining effect was seen from this film. The HYAFF 11 p50 film also resulted in low concentrations (10–20 μg/ml). The absence of an initial high peak concentration resulted in a low total $AUC_{0-8\,h}$. While we would expect this film to provide a higher total $AUC_{0-8\,h}$ than the HYAFF 11 p75 film based on their relative hydrophilicities, our findings did not support this. The result seen may be an experimental artifact due to the observed lack of retention of the film in the rabbit eye for the entire study period. Such lack of retention may be due to excessive swelling of the film in the ocular fluids and would result in a lower 'mean AUC'. In this case, an apparently ideal contribution of the early (28%) and late (72%) phases to the total AUC may not be of much value from a standpoint of therapeutic efficacy. These results seem to suggest that the two hydrophilic polymers afford poor control over drug release. A higher drug loading in the films would probably 'raise' the entire in vivo release profile and provide adequately high drug levels in the later phases of the tear fluid curve. However, potential irritation and toxicity resulting from the higher drug loading should be an inherent consideration in such strategies. The HYAFF 11 p75 and HYAFF 11 films both provided comparable $AUC_{0-8\,h}$ values (Table 1). The concentration profile following the HYAFF 11 p75 film showed greater fluctuation, being high (100 μg/ml) at the earlier time points and falling to levels lower than 30 μg/ml about 3 h post-dosing. A relatively even distribution was seen in the early and late contributions to the total AUC. On the other hand, the HYAFF 11 film was seen to maintain steady tear fluid prednisolone concentrations (45–72 μg/ml) over the entire study period (Fig. 2) without the high initial levels seen with the other films. The first 2 h accounted for 29% of the total AUC while the remaining 6 h accounted for 71%. Thus, the HYAFF 11 film appeared to provide the best combination of sustained release and total precorneal drug exposure among the films studied.

Table 1
Total AUCs (0–8 h) obtained following administration of test films in the rabbit eye, and percent contributions of the early (0–2 h) and late (2–8 h) phases of the tear fluid profiles to the total AUC

Dosage form	Total $AUC_{(0-8\,h)}$ (μg min ml^{-1}) ±SE ($\times 10^3$)	$AUC_{(0-2\,h)}$ [a] as percent of total $AUC_{(0-8\,h)}$	$AUC_{(2-8\,h)}$ [b] as percent of total $AUC_{(0-8\,h)}$
HYAFF 11 film	19.9 ± 7.1	29	71
HYAFF 11 p75 film	24.3 ± 5.3	45.2	54.8
HYAFF 11 p50 film	11.6 ± 2.6	28	72
HYAFF 11 p25 film	65.0 ± 13.0	85	15

[a] Calculated on the basis of mean tear fluid concentrations of prednisolone between 0 and 2 h.
[b] Calculated on the basis of mean tear fluid concentrations of prednisolone between 2 and 8 h.

This reflects observations that were made by Kyyrönen et al. (1992), when HYAFF 11 films containing physically dispersed methylprednisolone were found to provide high total AUC as well as sustained tear fluid drug concentrations (70–100 μg/ml) for 8 h.

Drug release in vivo was seen to depend qualitatively on the hydrophilicity of the polymer used to make the film, because this property determines the rate of permeation of solvent into the matrix and hence its hydration (Hunt et al., 1990; Papini et al., 1993). The effect of hydration is exaggerated in situations like the current study where the amount of 'solvent', namely, the tear fluid available for hydrating the film is very small. The more hydrophilic HYAFF 11 p25 and HYAFF 11 p50 polymers which have only 25 and 50%, respectively, of their carboxylic groups esterified, are thus expected to have faster hydration rates and hence a faster overall release rate. On the other hand, the HYAFF 11 p75 (75% of the carboxylate groups esterified) and HYAFF 11(100% of the carboxylate groups esterified) being more hydrophobic in nature are expected to have slower hydration rates and hence a slower exposure of the dispersed drug to the tear fluid. A fast initial release rate would result in lower tear fluid concentrations because of high tear fluid turnover and in higher variability due to external factors such as blinking rates. However, a release rate that is too slow would also be ineffective because the rapid elimination of drug would not allow therapeutic concentrations to be attained. AUCs in general provide a good measure of the overall target organ exposure to the drug. Since they reflect the high concentration peaks normally seen in ocular pharmacokinetics, they proved to be a useful tool to compare in vivo release rates from the various films in our study.

In conclusion, HYAFF 11 provided a suitable matrix material for a film containing physically dispersed prednisolone. It was anticipated that the degree of esterification and polymer hydrophilicity would have a discernable effect on the release of prednisolone from the films. The in vivo results qualitatively suggest that the lower hydrophilicity plays an important role in retarding the release of the drug from the HYAFF 11 films. While such formulations need to be optimized, prolonged release may be obtained from more hydrophilic polymers by using higher drug loading levels. Thus, adequate delivery of prednisolone to the eye may be achieved with the use of various hyaluronic acid esters by manipulation of polymer hydrophilicity.

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